REMARKS

Amendments

Claim 1 is amended to recite a person without cardiovascular disease or without a diagnosis thereof (e.g. Specification, p.1, lines 31-32); claims 1-6 are amended to improve form and antecedence; these amendments do not alter the scope or subject matter of the claims, and introduce no new matter.

37CFR1.75(d)(1)

Specification support for "a third value different from said first and second risk values" is found in original claim 11 of the application as filed; see also, Specification, p. 3, lines 1-5 and p. 6, lines 13-15.

35USC112, second paragraph

The test for determining whether a claim complies with the definiteness requirement is whether the claim as a whole apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function of the patent claim.

What is "a person without cardiovascular disease or without a diagnosis thereof" is self-evident to one skilled in the art, and the use of the phrase in the Specification (e.g. p.3, lines 8-13) and Claims is consistent with how one skilled in the art would understand this term. One of ordinary skill in the art (e.g. a cardiovascular health professional) would understand the metes and bounds of this phrase.

What is an "apparently healthy individual" as recited in the preamble of claim 7 is self-evident to one skilled in the art, and the use of the phrase in the Specification (e.g. p.3, lines 9-13) and Claims is consistent with how one skilled in the art would understand this term. One of ordinary skill in the art (e.g. a cardiovascular health professional) would understand the metes and bounds of this phrase.

What is meant by the phrase "characterizing the individual's risk of developing the cardiovascular disorder based upon the combination of the first risk value and the second risk value, wherein the combination of the first risk value and second risk value establishes a third risk value different from said first and second risk values" is evident to one skilled in the art in view of the Specification (e.g. p. p. 3, lines 1-5 and p. 6, lines 13-15). One of ordinary skill in

the art (e.g. a cardiovascular health professional) would understand the metes and bounds of this phrase.

Attached is a an expert Declaration under 37CFR1.132 averring to the foregoing, and confirming that the claims are sufficiently clear such that one of ordinary skill in the art to which the invention pertains would understand the metes and bounds of the claims and be on notice as to what is the scope of the claims.

35USC112, first paragraph (enablement)

The test for enablement is whether the specification would have enabled one skilled in the art to practice the invention as claimed without undue experimentation. The specification need not disclose, and preferably omits what was well-known to those skilled in the art.

The invention of claim 1 comprises a two-step method of determining cardiovascular risk in a person without cardiovascular disease or without a diagnosis thereof: (i) determining a test MIF concentration in the blood, saliva or urine of the person as a marker of cardiovascular risk for the person, wherein an elevated test MIF concentration compared with a control MIF concentration not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk, and (b) a further step selected from the group consisting of: (a) assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration; (b) prescribing for the person a cardiovascular treatment modality in accordance with the test MIF concentration; and (c) making an additional assessment of cardiovascular risk of the person in accordance with the test MIF concentration, the additional assessment selected from the group consisting of a stress test, a CRP assay and an LDL assay. The Specification plainly enables this two-step method:

(i) As taught in the Specification, MIF levels can be determined by a variety of art recognized methods:

> Typically, the level is determined by measuring the level of the marker in body fluid, such as blood, saliva or urine. The level can be determined by immunoassay or other techniques for determining the presence of the marker. A commercial human MIF ELISA detection kit is available from Chemicon (Temecula, Calif.), now Serologicals Corp. (Atlanta, Ga.). Automated analyzers on which tests for MIF can be performed include Dade Behring BN II Plasma Protein System (Dade Behring, Incorporated, Deerfield, Ill., USA), Abbott Laboratories IMx Immunoassay Analyzer (Abbott Laboratories, Abbott Park, Ill., USA), IMMULITE (Diagnostics Products Corporation, Los Angeles, Calif., USA), and

> IMMAGE (Beckman Coulter, Inc., Fullerton, Calif., USA). The Dade Behring BN II assay utilizes a monoclonal antibody on a polystyrene particle with fixed-time nephelometric measurements. The Abbott IMx assay is a two-site chemiluminescent enzyme immunometric assay with one monoclonal and one polyclonal anti-MIF antibody. The Beckman Coulter IMMAGE assay uses a polyclonal anti-MIF antibody on latex particles with rate nephelometric measurements. Specification p. 3, line 29 – p. 4, line 10.

The Specification plainly enables one skilled in the art to practice this step without undue experimentation.

(ii) (a) Taken in context, the claims recite "assigning to the person a cardiovascular risk metric *in accordance with his/her MIF concentration*". This step requires no more than assigning to the person a metric proportional to his/her MIF concentration (e.g. Specification, p.2, lines 16-17). The particular form of metric used is discretionary to the practitioner; e.g. numerical metrics such as "risk level 1, risk level 2, etc" or more descriptive metrics such as "very high risk, high risk, normal risk, low risk, etc." In view of the Specification, one skilled in the art is well-enabled to practice this step without undue experimentation.

(ii) (b) Prescribing a person a cardiovascular treatment modality in accordance with the person's risk of cardiovascular disease is routine in the art; for example, a person having an elevated MIF concentration may be treated with anti-inflammatory therapies; e.g. Specification p. 4, lines 22-25.

(ii) (c) The recited stress test, CRP assay, and LDL assay are also well-known and routine to those skilled the art; e.g. see the attached abstracts of Kurl et al, Stroke (2001) 32:2036-41; and St. Pierre et al. Am. J. Cardiol (2003) 91:555-8. In view of the Specification, one skilled in the art is well-enabled to practice this step without undue experimentation.

The record demonstrates that the Specification enables one skilled in the art to practice the two-step method of Claim 1 without undue experimentation.

The invention of Claim 7 comprises a three-step method for characterizing a risk of developing a future cardiovascular disorder in an apparently healthy individual. The recited obtaining and comparing steps use the same methodology as the determining step of Claim 1, and are demonstrably readily practiced by one skilled in art without undue experimentation (supra). The third recited step, characterizing an individual's risk of developing a cardiovascular disorder based on his/her level of a cardiovascular disease marker (MIF) is similarly readily practiced without undue experimentation. This step requires no more than assigning to the

person a metric proportional to his/her MIF concentration (e.g. Specification, p.2, lines 16-17). The particular form of metric used is discretionary to the practitioner; e.g. numerical metrics such as "risk level 1, risk level 2, etc" or more descriptive metrics such as "very high risk, high risk, normal risk, low risk, etc." In view of the Specification, one skilled in the art is well-enabled to practice this step without undue experimentation. The Specification provides the requisite teaching that elevated levels of MIF in apparently healthy persons are predictive of future cardiovascular disorders (e.g. p. 2, lines 26-28).

The invention of Claim 15 is a two-step method for evaluating the likelihood that an individual will benefit from treatment with an agent for reducing the risk of a cardiovascular disorder. The recited obtaining and comparing steps use the same methodology as the determining step of Claim 1, and are demonstrably readily practiced by one skilled in art without undue experimentation (supra). The Specification provides the requisite teaching that MIF is elevated in patients with high cardiovascular risk, and that it falls when interventions are made which reduce the risk (e.g. Specification, p. 1, lines 29-31), i.e. that the test MIF level is indicative of whether the individual will benefit from treatment with the agent.

Attached is an expert Declaration under 37CFR1.132 averring to the foregoing, and confirming that one of ordinary skill in the art would be able to practice the claimed invention without undue experimentation.

35USC112, first paragraph (written description)

The Written Description test is whether the Specification reasonably conveys possession of the invention as claimed to those skilled in the art. Here, the Action objects to the words "test" and "control". As recently restated by the Federal Circuit:

> In order to comply with the written description requirement, the specification "need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that as of the [filing] date the applicant had invented what is now claimed." [cites omitted] All Dental Prodx, LLC v. Advantage Dental Prods, Inc., 309 F.3d 774, 779 (Fed. Cir. Oct 2002).

The invention is a method of determining cardiovascular risk in a person not predetermined to be subject to cardiovascular disease by determining the MIF concentration in the blood, saliva or urine of the person as a marker of cardiovascular risk for the person. The

concept of a "marker of cardiovascular risk" implies to one skilled in the art that the marker is different in the risk group and in a corresponding control group. Furthermore, what you call the measure from the examined person ("test", "subject", etc.) and what you call the compared-to measure ("control", "predetermined value", etc.) are arbitrary and self-evident, inherent measures required for a disease "marker":

> The invention provides methods for characterizing an apparently healthy individual's risk of, and/or developing their risk profile for developing a future subject cardiovascular disorder. The method comprises obtaining a level of MIF in the individual, typically expressed as MIF concentration, and comparing the level of the marker to a predetermined value. The individual's risk or risk profile of developing a future subject cardiovascular disorder then is characterized based upon the level of the marker in comparison to the predetermined value. Specification, p.3, lines 14-20.

The recited predetermined value is a control:

> The predetermined value will depend upon the characteristics of the patient, and/or the relevant patient population. The predetermined value can be a single value, multiple values, a single range or multiple ranges. Thus, in one embodiment, the predetermined value is a plurality of predetermined marker level ranges, and the comparing step comprises determining in which of the predetermined marker level ranges the individual's level falls. In another embodiment, the predetermined value is a historical value from the patient. Specification, p.4, lines 11-16.

Though not required, the Specification even expressly refers to the compared-to or "predetermined value" a "control":

> I. Comparison of MIF and CRP levels as correlates to reductions in cardiovascular risk. This study was designed to compare MIF and CRP as markers correlating with cardiovascular risk.
> Methods: In an initial demonstration, we monitored MIF in obese adults, with very high cardiovascular risk, who were subjected to a one-year regimen of diet and exercise.
> Results: We found that MIF levels tracked progress (reduction in cardiovascular risk) through the treatment regimen better than did CRP. In our ***control*** group (n=83), MIF levels were 38 +/- 16 ng/ml. The obese patients at baseline are elevated to 100+ ng/ml generally and drop to normal levels generally after 1 year. Specification, p.5, line 7 (emphasis added)

That the determined MIF concentration is a "test", and the compared-to value is a "control" is both self-evident and inherent in the original claims. The Specification plainly conveys possession of the invention as claimed to those skilled in the art.

35USC102

Yabanuka et al. (Diabetes Care 2000, 23; 2, 256-58) "examined the concentration of serum MIF in type 2 diabetes to clarify the possibility that MIF is associated with the disregulation of glucose metabolism." p.256, sentence bridging cols. 1, 2 .

The authors report mixed findings: "The serum MIF level was elevated as the clinical stage of diabetic retinopathy advanced, but that was low in the proliferative stage (Fig.2). The serum MIF did not differ with the clinical stage of diabetic nephropathy and neuropathy." p.256, col.3, lines 16-22.

The authors speculate on possible explanations: "It is speculated that MIF stimulates insulin secretion and MIF secretion is regulated by glucose. It may be reasonable that MIF seems to modulate the carbohydrate metabolism as MIF modulates the inflammatory and immunological responses, counterregulating impaired homeostasis by the action of glucocorticoid suppression." p.257, col.2, lines 81-6.

The authors conclude that MIF is not a specific disease marker, but a nonspecific marker for illness in general: "Increased serum MIF may be another nonspecific marker for illness in general, rather than a key player in the pathogenesis of type-2 diabetes. In fact, MIF was increased in the sera of patients with uveitis and atopic dermatitis.... p.257, col.3, lines 12-17.

Claim 1 recites a method of determining cardiovascular risk in a person without cardiovascular disease or without a diagnosis thereof, the method comprising the step of determining a test MIF concentration in the blood, saliva or urine of the person as a marker of cardiovascular risk for the person, wherein an elevated test MIF concentration compared with a control MIF concentration not associated with cardiovascular risk indicates that the person is subject to elevated cardiovascular risk, and a further step selected from the group consisting of: (a) assigning to the person a cardiovascular risk metric in accordance with the test MIF concentration; (b) prescribing for the person a cardiovascular treatment modality in accordance with the test MIF concentration; and (c) making an additional assessment of cardiovascular risk

of the person in accordance with the test MIF concentration, the additional assessment selected from the group consisting of a stress test, a CRP assay and an LDL assay.

Yabanuka et al. neither teach nor suggest the claimed two-step method. Yabanuka et al. do not suggest that MIF is a marker for cardiovascular risk. To the contrary, they suggest it is not useful as any specific disease marker, but rather is a non-specific marker for illness in general. Since Yabanuka does not teach or suggest that MIF is a marker of cardiovascular risk, the reference can not anticipate our claims.

Yabanuka does not assign to each subject person a cardiovascular risk metric in accordance with their test MIF concentration. Nowhere does Yabanuka assign to any subject person anything *in accordance with his/her test MIF concentration.* Yabanunka's subjects are predetermined to have type 2 diabetes, and they are never assigned any measure of cardiovascular risk in accordance with their test MIF concentrations.

Yabanuka does not teach or suggest prescribing a cardiovascular treatment modality to any subject person *in accordance with his/her test MIF concentration.*

Yabanuka does not teach or suggest making an additional assessment of cardiovascular risk of a subject person *in accordance with his/her test MIF concentration.*

Since Yabanuka does not teach or suggest assigning a cardiovascular risk metric or prescribing a cardiovascular treatment modality or making an additional assessment of cardiovascular risk *in accordance with an assayed MIF concentration,* as recited in claim 1, the reference can not anticipate our claims.

Related inventor publication

The undersigned became aware on Dec 12, 2006 of a related pre-filing date publication coauthored in part by some of the inventors; see attached Garner et al, Am J Physiol Heart Circ Physiol 285: H2500-H2509, 2003; first published Aug 28, 2003; 10.1152/ajpheart.00432.2003.

To obviate this reference, we attached a 131 Declaration swearing behind this publication. The 131 Declaration provides an attached draft of the subject application that was prepared prior to the publication of Garner et al., demonstrating that referenced publication is not prior art under 25USC102.

The Examiner is invited to call the undersigned if he would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language. Please charge our Deposit Account No.19-0750 (order UTSD:1477) any fees, necessary extensions of time, or credit any overcharges relating to this communication.

Respectfully submitted,
Science & Technology Law Group

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Encl. Declaration under 37CFR1.132
Declaration under 37CFR1.131, including Aug 19 Draft Application
Garner et al, Am J Physiol Heart Circ Physiol 285: H2500-H2509, 2003
Kurl et al, Stroke (2001) 32:2036-41 (abstract)
St. Pierre et al. Am. J. Cardiol (2003) 91:555-8 (abstract)

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